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Spice plant *Allium cepa*: Dietary supplement for treatment of type 2 diabetes mellitus

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ABSTRACT

Objective: Diabetes mellitus (DM) is associated with significant morbidity and mortality and its prevalence is increasing worldwide. Although conventional antidiabetic agents are known to ameliorate the symptoms of diabetes, they also may cause adverse effects. The purpose of this review was to organize and discuss various studies that have been previously conducted indicating the efficacy of *Allium cepa* in DM.
Methods: A comprehensive English literature search was conducted using various electronic search databases. Different search terms were used and an advanced search was conducted by combining all the search fields in abstracts, keywords, and titles.
Results: Allium cepa, a spice plant, is commonly known as onion and belongs to the family liliaceae. Since ancient times, it has been used traditionally for the treatment of different diseases. Among various activities of *Allium cepa*, regulation of hypoglycemic activity is considered one of its important effects in DM. Sulfur compounds including *S*-methylcysteine and flavonoids such as quercetin are mainly responsible for the hypoglycemic activity of *Allium cepa*. *S*-methylcysteine and flavonoids help to decrease the levels of blood glucose, serum lipids, oxidative stress, and lipid peroxidation, as well as increasing antioxidant enzyme activity and insulin secretion. Extracts of onion also have been shown to have hypoglycemic and hypolipidemic effects by normalizing the activities of liver hexokinase, glucose 6-phosphatase and HMG coenzyme-A reductase. In preliminarily clinical trials, patients with diabetes safely consumed slices of *Allium cepa*, exhibiting sufficient hypoglycemic activity. In the future, further studies must be conducted to investigate and confirm the hypoglycemic activities of *Allium cepa* and its constituents and/or their synthetic analogs.
Conclusion: This review will not only elucidate the nutritious facts of *Allium cepa* but may also help in understanding the molecular basis of its effects in DM. This review will explore in particular the medicinal characteristics of *Allium cepa* supporting that the consumption of dietary onion could lower blood glucose levels, thus contributing to the reduction of risk factors associated with DM.

Introduction

Diabetes mellitus (DM) is a serious chronic and heterogeneous disease of diverse disorders affecting the metabolism of proteins, fat, and carbohydrates [1,2]. Major factors that contribute to the prevalence and progress of DM include hyperglycemia, dyslipidemia, insulin resistance, impaired insulin secretion, and the activation of proinflammatory mediators [2,3]. DM is considered one of the most frequent lifestyle diseases [4].

Type 2 diabetes mellitus (T2DM) is known as non-insulin–dependent diabetes mellitus in which resistance to insulin, abnormal insulin secretion, elevated levels of insulin, or all three have been observed. Among diabetic cases diagnosed, >95% are T2DM [2]. Existing conventional and synthetic antidiabetic

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agents for the treatment of T2DM are well known for potential adverse effects such as weight gain, acute hypoglycemia, edema, hepatic and cardiac defects, and gastric and respiratory complications [2], which have motivated researchers and scientists to investigate new avenues for the treatment of DM [5–11]. One area being researched is the therapeutic use of medicinal plants that have shown hypoglycemic properties. Herbal plants are less toxic and free from side effects compared with synthetic drugs [12,13], which are restricted in terms of efficacy and side effects [2,14,15]. In Asian communities, herbal agents are most commonly used as an effective remedy for the treatment of many diseases [16–18]. Use of medicinal plants for treatment of DM is most important where resources are meager and insufficient [19–24]. The families of plants that have shown potent hypoglycemic effects include Leguminoseae, Lamiaceae, Liliaceae, Cucurbitaceae, Asteraceae, Moraceae, Rosaceae, Euphorbiaceae, Araliaceae and Ranunculaceae [19,25,26].

In this present study, we have summarized general properties of *Allium cepa*. To understand the molecular basis of its effects in DM, we explore *Allium cepa's* medicinal characteristics by discussing various experimental studies performed to identify the hypoglycemic properties of onion, its extracts, juices, essential oils, and constituents. Here, we have tried to confirm that consumption of dietary onion could help lower blood glucose levels, thus contributing to a reduction in risk factors associated with DM.

Methods

A comprehensive online English literature search was conducted via electronic databases including Medline, PubMed, EMBASE, and Scopus (1973–2014). Initially, searched terms like *antidiabetic agent*, *onion*, *Allium cepa*, *flavonoids such as quercetin*, *sulfur compounds such as S-methylcysteine*, *type 2 diabetes mellitus*, *hypoglycemic effects of onion and/or Allium cepa*, *apoptosis*, *antidiabetic effects of onion and/or Allium cepa*, *biological properties of onion and/or Allium cepa*, *clinical trials*, *medicinal uses of onion and/or Allium cepa*, and *type 2 diabetic animal models used for the investigations of antidiabetic effects of onion and/or Allium cepa* were used. We combined all search fields in keywords, abstracts and/or titles for an advanced search. Using these search terms, appropriate articles were selected and for a comprehensive review, investigation of literature was further supplemented by searching the referenced articles created by original investigators. Finally, all the selected articles were confirmed for duplications. These were excluded if duplication was observed.

Results

General properties of Allium cepa

Allium cepa, commonly known as onion, is a bulbous plant that is widely cultivated in almost every country of the world, with its largest production in China, India and United States [12,27]. *Allium cepa* is a spice plant that belongs to the family liliaceae and contains many essential nutrients (Table 1). This herbaceous species also has been used in stomach disease, cholera, throat infection, and hepatitis. Pharmacologically, onion is recognized as an anti-asthmatic, antihypertensive, antihyperglycemic, and antioxidative agent [28–30].

Allium cepa contains various chemicals that have distinctive biological activity. Until recently, seven compounds such as tianshic acid, *N*-trans-feruloyltyramine, beta-sitosterol-3 beta-glucopyranoside-6'-palmitate, sitosterol, daucosterol, tryptophan, and adenine riboside have been isolated from the seeds of *Allium cepa* via ethanolic extract [31]. Various sugars, including glucose, fructose, sucrose, and an oligosaccharide containing a ketose portion, also have been identified in 80% ethanolic extracts of *Allium cepa* [32].

The essential oil of *Allium cepa* contains 30 compounds of which 3—1,8-cineole, L-linalool, and camphor—are considered toxic. These toxic compounds act as a larvicidal agent [33]. The onion bulb exhibited an ecobolic effect in rats because of the presence of Kaempferol, β-sitosterol, ferulic acid, myritic acid, and prostaglandins [29,34]. Flavonoids and tannins present in *Allium cepa* have shown wound-healing activity [34]. High concentrations of quercetin, quercetin 4-glucoside, taxifolin, taxifolin 7-glucoside, and phenylalanine have been isolated from the red bulbs of *Allium cepa* [35]. Quercetin, a major phenolic content in onion, inhibits the liberation of D-glucose from oligosaccharides and disaccharides by inhibiting α-glucosidase, resulting in delayed absorption of glucose from the intestine and is thereby considered responsible for controlling blood glucose levels [36,37]. Onionin A is a new, stable, sulfur-containing compound isolated from acetone extracts of bulbs of *Allium cepa*. Its structure has been characterized as 3,4-dimethyl-5-(1 E-propenyl)-tetrahydrothiophen-2-sulfoxide-*S*-oxide, on the basis of the results of spectroscopic analysis. This compound illustrated the ability to suppress tumor cell proliferation by inhibiting polarization of alternatively activated macrophages, M2 [38].

The major sulfur compounds present in onion are dimethyl trisulfide, propenyl propyl disulfide, dipropyl disulfide, propenylmethyldisulfide and methyl propyl trisulfide dipropyle trisulfide [4]. Onion contains active compounds such as allyl propyl disulfide along with other active sulfur-containing compounds. Thereby, the hypoglycemic property of onion may be due to the presence of sulfur compounds as well as flavonoids such as quercetin.

Table 1
Nutritional values of different nutrients in 100 g of onion

Nutritional value of *Allium cepa* (onion) per 100 g	
Nutrient	Quantity
Water	89.11 g
Carbohydrates	9.34 g
Dietary fiber	1.7 g
Protein	1.1 g
Fat	0.1 g
Thiamine (vitamin B_1)	0.046 mg
Riboflavin (vitamin B_2)	0.027 mg
Niacin (vitamin B_3)	0.116 mg
Vitamin B_6	0.12 mg
Vitamin C	7.4 mg
Vitamin E	0.02 mg
Calcium	23 mg
Iron	0.21 mg
Magnesium	0.129 mg
Phosphorus	29 mg
Potassium	146 mg
Sodium	4 mg
Zinc	0.17 mg
Folate (vitaminB_9)	19 μg
Vitamin K	0.4 μg

Source: USDA Nutritional database

Antidiabetic activity of Allium cepa *in alloxan-induced diabetic animal models*

One study [39] investigated the hypoglycemic and antioxidant effects of *S*-methylcysteine sulfoxide (SMCS), a major component of onion, using alloxan-induced diabetic rats. The researchers used 200 mg/kg body weight of SMCS for 60 d. SMCS significantly ameliorated the diabetic conditions similar to that of two standard drugs (glibenclamide and insulin). Moreover, SMCS also exhibited antioxidants on lipid peroxidation in experimental animals.

Another study [40] investigated the hypoglycemic effects of onion and garlic juice on alloxan-induced diabetic rats. In this study, a significant increase was observed in the plasma levels of glucose, urea, creatinine, and bilirubin in alloxan-induced diabetic rats. Plasma aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and acid phosphatase also were significantly increased in alloxan-induced diabetic rats. The lactate dehydrogenase activity in diabetic rats was increased in the brain compared with that of normal rats. The concentration of thiobarbituric acid reactive substances and the activity of glutathione *S*-transferase in plasma, liver, testes, brain, and kidneys also were significantly increased in diabetic rats compared with normal rats. After 4 wk of treatment with onion, garlic juice, or both (1 mL/100 g body weight), significant antioxidant and antihyperglycemic effects were observed in treated rats. These juices also alleviated liver and renal damage in alloxan-induced diabetic rats. In this study, equal volumes of both juices were administered, however, onion juice showed a more pronounced antioxidant and antihyperglycemic effect compared with garlic juice, suggesting the potential hypoglycemic effect of *Allium cepa*.

The hypoglycemic effects of *Allium cepa* were investigated along with two other plants (garlic and ginger) [41]. Three different doses of aqueous extracts of plants according to body weight (i.e., 200, 250, and 300 mg/kg) were administered to alloxan-induced diabetic rats. At the end of treatment, the results showed that aqueous extract of *Allium cepa* exhibited dose-dependent hypoglycemic effects. The ability of onion extract to lower blood glucose levels was probably due to the presence of bioactive compounds that may enhance glucose uptake in peripheral tissues by improving insulin sensitivity and/or secretion, and by increasing the activity of NADP+ and NADPH ratio. Alloxan is known to cause damage of pancreatic islets, whereas aqueous extract of onion could sufficiently heal this damage and improve insulin secretion in response to glucose, which is evident from decreased blood glucose levels observed in previously published reports [27,41]. The mechanism involved in the reduction of blood glucose levels still needs to be elucidated.

A recent study [30], investigated the hypoglycemic, antioxidant, and hepatoprotective effects of aqueous extracts of *Allium cepa* on alloxan-induced diabetic rabbits. DM was induced in 15 adult male rabbits by administering an intraperitoneal single injection of alloxan monohydrate (200 mg/kg). After dividing these alloxan-induced diabetic rabbits into three groups, they were then given separate treatments. The first group received 100 mg/kg of oral aqueous extract of *Allium cepa* daily for 30 d. The second group received 300 mg/kg oral *Allium cepa* daily for 30 d and group 3, the diabetic control group, was given peanut oil as a vehicle. Another group comprising of five rabbits were kept as a negative control group and did not receive alloxan or *Allium cepa*. In the study, *Allium cepa* was observed to be capable of attenuating the liver histologic derangements induced by alloxan injection. Moreover, a dose-dependent increase in the efficacy of *Allium cepa* was seen in terms of blood glucose levels along with an increase in the levels of endogenous antioxidant enzymes. Additionally, an increase in the level of malondialdehyde (MDA) indicated a reduction in lipid peroxidation by *Allium cepa*. This study clearly demonstrated the hepatoprotective role of *Allium cepa* in diabetic-associated liver toxicity along with a remarkable improvement of blood glucose levels.

The studies discussed here provide clear evidence that *Allium cepa* targets hyperglycemia by improving insulin secretion and increasing the cellular uptake of glucose, which can be partly attributed to one of its active constituents, SMCS.

Antidiabetic activity of Allium cepa *in streptozotocin-induced diabetic animal models*

In one study [42], freeze-dried onion powder (3%) was used to investigate the antidiabetic effects of *Allium cepa* on streptozotocin (STZ)-induced diabetic rats for 8 wk. At the end of the treatment period, dried onion significantly exhibited its antihyperglycemic and antihyperlipidimic effects compared with a diabetic control group. Diabetic rats fed dried onion powder also exhibited low lipid peroxide levels compared with the diabetic control group. Overall, the dried onion powder significantly improved the metabolic status of DM by exerting its hypoglycemic and hypolipidemic effects.

The antioxidative and anti-inflammatory effects of quercetin, which is considered the most potent and active constituent of *Allium cepa* on β-cell damage, were investigated using STZ-induced diabetic rats [43]. Quercetin (15 mg/kg) was administered daily for 4 wk. At the end of the treatment period, quercetin significantly increased the activities of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase (SOD), and catalase in pancreatic islets; however reduced values of serum nitric oxide (NO) and pancreatic tissue MDA indicated a reduction in lipid peroxidation. The study also included immunohistochemical analysis using anti-insulin antibody to investigate the antioxidative effects of quercetin on pancreatic β cell. STZ-induced diabetic rats with no treatment showed shrunken pancreatic islets having necrotic and degenerative changes,

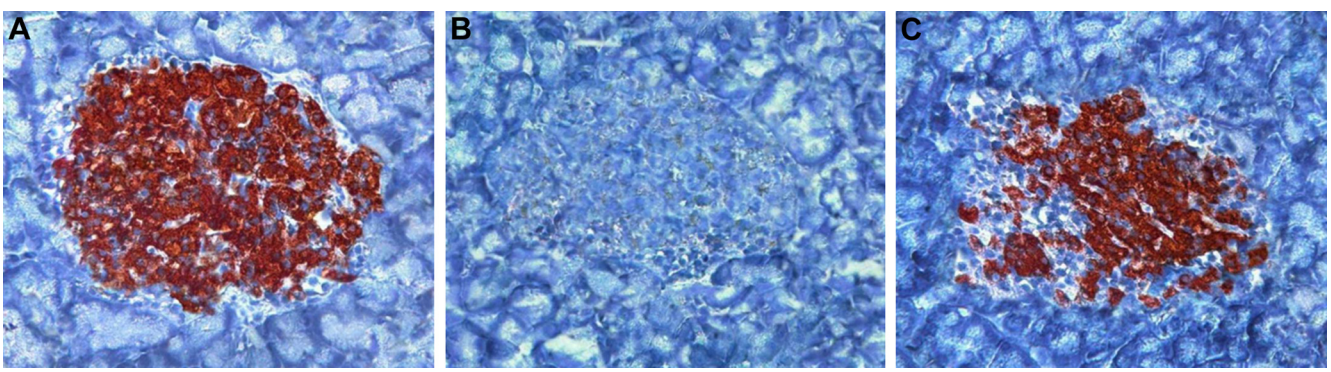

Fig. 1. Immunohistochemical results of β-cells of pancreatic islets (A–C). Coexhibits normal architecture of islets of pancreas showing β-cells in the islets of pancreas that are strongly stained with anti-insulin antibody (A). Shrunken islets of pancreas that exhibit necrotic and degenerative changes in streptozotocin (STZ)-induced diabetic rats with no treatment (B). Normal architecture of islets of pancreas in STZ-induced diabetic rats that were treated with quercetin that are more or less similar to control (C). Adapted from reference 43.

whereas quercetin-treated rats exhibited strong staining of insulin and normal morphology of pancreatic islets compared with control (Fig. 1). The significant results of this study demonstrated that quercetin has strong antioxidative activity that can protect β cells of pancreatic islets from deleterious effects of STZ and increases the levels of antioxidative enzymes up to significant extent.

Another study [44] investigated the antioxidative effects of onion diet on STZ-induced diabetic rats and compared its effects with equivalent amounts of quercetin aglycone. The activity of antioxidant enzyme in treated animals was measured after a 12-wk treatment period with onion and/or equivalent amount of quercetin aglycone. STZ-induced diabetic rats treated with the onion diet showed significantly decreased levels of glucose in plasma with increased activity of antioxidant enzyme compared with nontreated rats or those treated with quercetin aglycone. Results from this study found that an onion diet has more potent antioxidant activity compared with that of quercetin alone, thus indicating that other then quercetin, there are few more essential constituents in *Allium cepa* that also may contribute to the induction of hypoglycemic effects.

The effects of the essential oil of *Allium cepa* on STZ-induced diabetic rats were investigated in another study [45]. Diabetes was induced by the subcutaneous injection of STZ and the animals were divided into three groups. Group 1 was the normal control, group 2 the diabetic control, and group 3 consisted of diabetic rats receiving *Allium cepa* essential oil orally with a dose of 100 mg/kg. After 21 d, the animals were fasted for 12 h. Thereafter, blood samples were collected and the serum was separated for measurement of glucose, insulin, various lipid profiles, NO, and lipid peroxidation. At the end of treatment, essential oil of *Allium cepa* was found to significantly improve the serum levels of insulin as well as to improve blood glucose levels. Essential oil of *Allium cepa* also significantly decreased various lipid profiles in treated rats. Reduction in serum levels of NO and lipid peroxidation was also observed in animals treated with essential oil of *Allium cepa*. The researchers also investigated the effects of essential oil on liver and kidneys and from histopathologic (Fig. 2) and histochemical (Fig. 3) analysis of liver and kidney they found that the rats treated with essential oil of *Allium cepa* showed similar histologic characteristics compared with the control group. These results clearly demonstrated that essential oil might sufficiently improve the glucose tolerance via increasing serum levels of insulin and decreasing levels of lipid profiles. Additionally, it also has been shown that the antioxidative and hypolipidemic activity of *Allium cepa* might suppress oxidative stress.

Keeping in mind the antidiabetic and antioxidative properties of onion, one group of investigators [46] used 1% onion peel extract (OPE) in STZ-induced diabetic rats for 45 d to investigate its antihyperglycemic and antioxidative properties. They also compared the antioxidative effects of OPE with vitamin C. OPE showed hypoglycemic effects and more potent antioxidative effects compared with vitamin C in STZ-induced diabetic rats.

Together, these studies give an effect of potential hypoglycemic and antioxidant activity of *Allium cepa* that can be

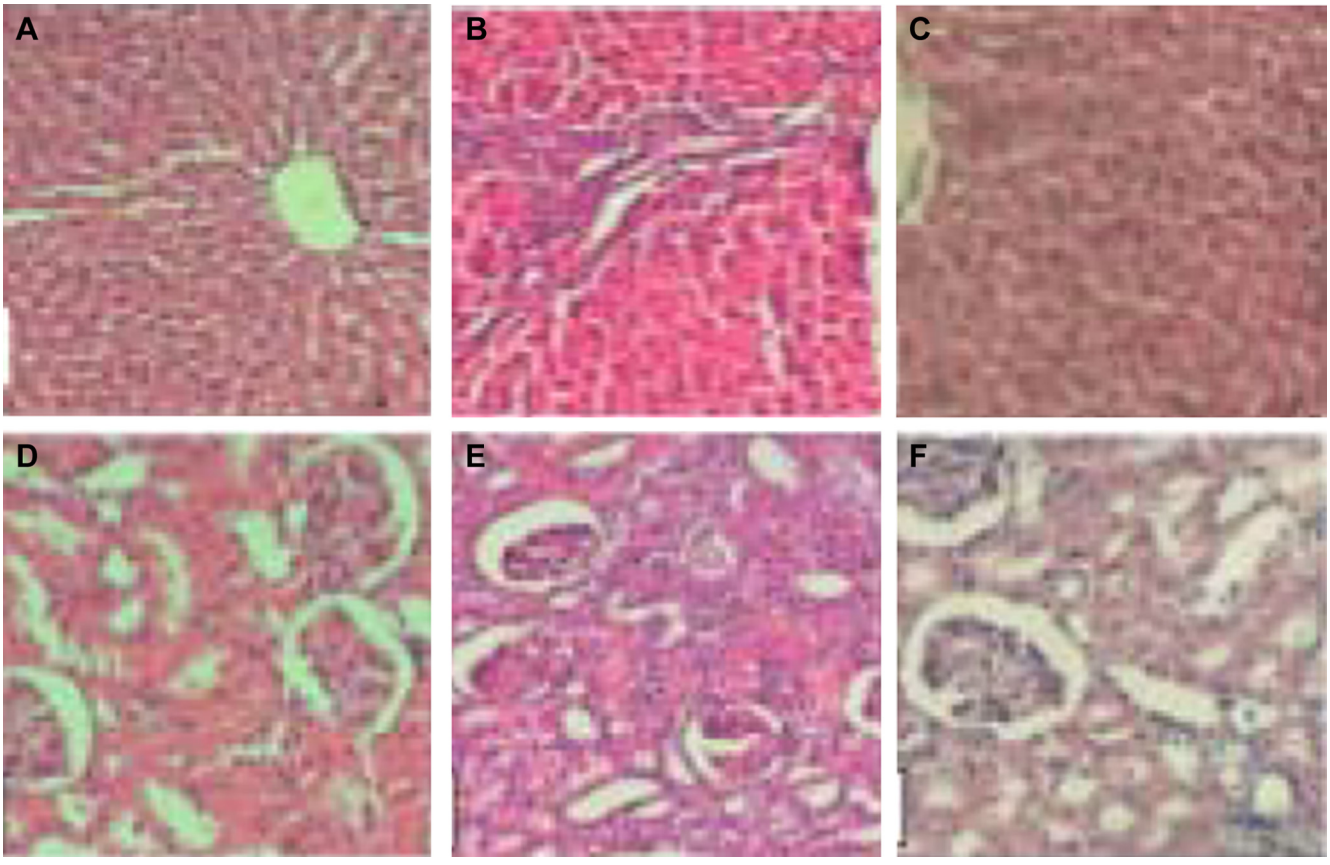

Fig. 2. Histopathological results of liver (A–C) and kidney (D–F). Normal structure of liver in control rats (A). Liver of diabetic rat that exhibits portal tract with dilated and congested veins associated with inflammation and (B). Diabetic rats treated with essential oil exhibit architecture of hepatic veins that are more or less like to control (C). Kidney of control rat that exhibit normal structure of glomeruli (D). Kidney of diabetic rat with increased mesangial cells and glomeruli (E). Kidney of diabetic rat treated with essential oil represents the structure more or less similar to control (F). Adapted from reference 45.

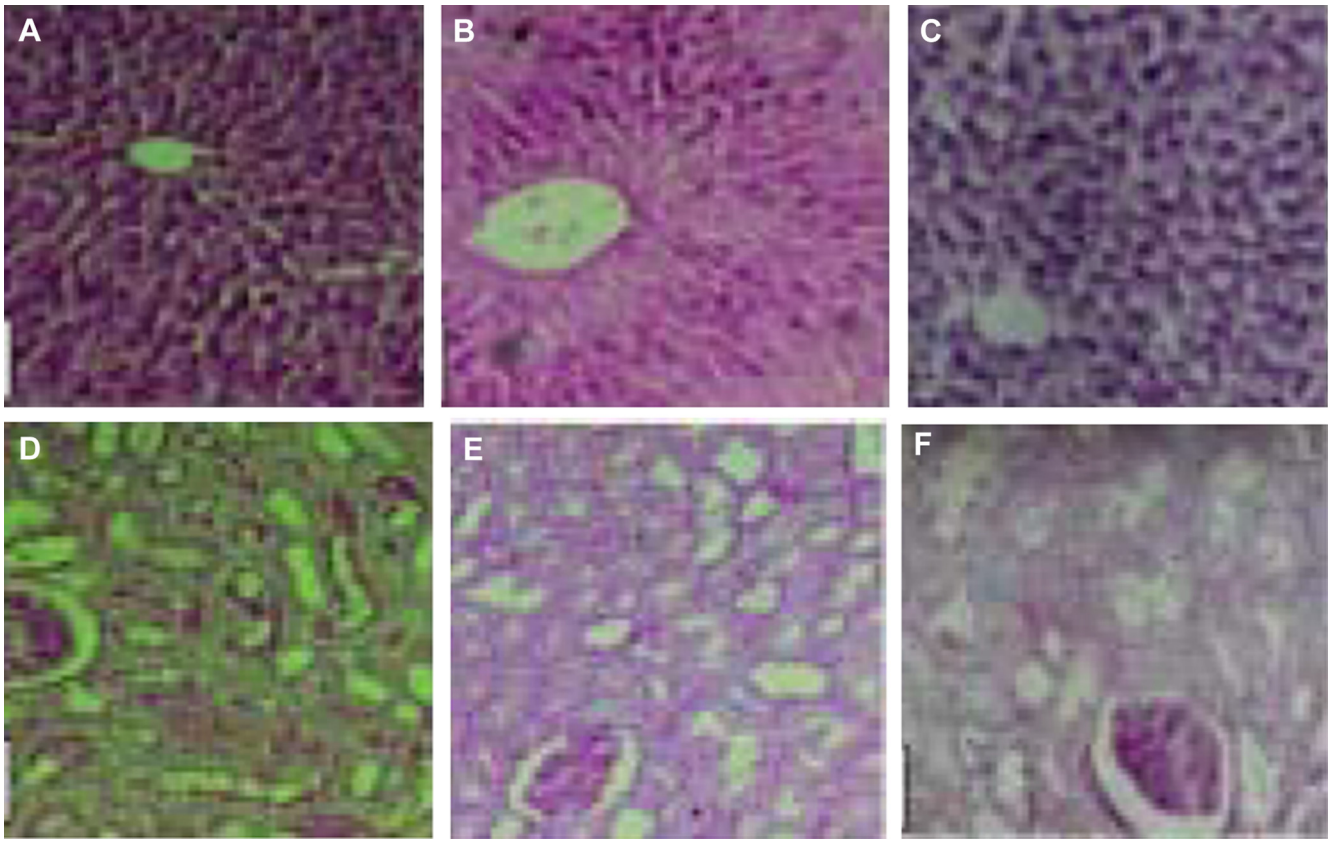

Fig. 3. Histochemical results of Liver (A–C) and kidney (D–F) exhibiting the polysaccharides. Liver of rat exhibiting the normal distribution of glycogen particle (A). Liver of diabetic rats exhibiting pericentral depletion of periodic acid Schiff's (PAS) +ve materials (B). Liver of essential oil–treated rat exhibits the distribution of glycogen more or less similar to control (C). Kidney of the control rat exhibits the normal distribution of polysaccharides in the form of PAS +ve materials in visceral walls of the Bowman's capsule, capillaries of the glomeruli, and basement membrane of the proximal (D). Kidney of diabetic rat exhibits an increased number of PAS +ve materials in mesangial cell and matrix of the glomeruli with increased thickness of basement membranes of the proximal and distal convoluted tubules (E). Kidneys of essential oil–treated rats exhibits the polysaccharides that appear more or less similar to control (F). Adapted from reference 45.

attributed to its essential constituents such quercetin derivatives and SMCS. Moreover, *Allium cepa* has the ability to protect the histologic and physiological characteristics of vital organs, including liver and kidneys.

Antidiabetic activity of Allium cepa *in Zucker diabetic fatty rats*

The antiobesity effects of onion extracts (3% and 5%) were investigated in Zucker diabetic fatty (ZDF) rats for a 28-d experimental study period [47]. The extract of onion significantly decreased the blood glucose and lipid profile of ZDF rats. Three percent onion extract could not exhibit its antidiabetic effects, whereas 5% onion extract helped to improve insulin sensitivity and decrease fasting blood glucose compared with the control group. The results of this study suggested that dietary onion can help ameliorate glucose intolerance and hyperlipidemia, as well as improve insulin sensitivity owing to the presence of its sulfur-containing compounds.

Hypoglycemic activity of Allium cepa *in high-fat diet/STZ-induced diabetic animal models*

Another group of researchers [48] investigated the antidiabetic effects of OPE on high-fat diet/STZ-induced diabetic rats. In this study, 1% OPE was used for 8 wk. The antidiabetic effects of OPE measuring glucose tolerance, insulin secretion, glucose uptake in peripheral tissues, plasma lipid profiles, biomarkers for oxidative stress and inflammation were investigated, along with the expression of genes for glucose transporter type (GLUT4) and insulin receptors (INsR) in skeletal muscles. In all cases, the researchers compared the effects of OPE with that of equivalent amounts of quercetin. From the experimental results, the researchers found that OPE sufficiently modulated the glucose uptake and metabolism in peripheral tissues via increased INsR and GLUT4 gene expression in skeletal muscles. Furthermore, OPE also improved the insulin sensitivity in peripheral tissues up to a significant extent by enhancing lipid metabolism in peripheral tissues and reducing hepatic oxidative and/or inflammatory stress. The enhanced lipid metabolism was observed with decreased values of plasma lipid profiles. Moreover, they assessed the oxidative stress by measuring SOD activity and MDA formation. The SOD activity was significantly increased whereas, the formation of MDA was significantly inhibited in OPE treated rats. Moreover, the hepatic inflammatory stress was assessed by tumor necrosis factor-α and interleukin-6, which also were significantly suppressed. From these results, the authors concluded that OPE is more potent compared with the equivalent amount of quercetin because OPE contains a greater percentage of polyphenols (64%) and of these, only 16% is quercetin. Similar types of results also have been found by quercetin showing antioxidative and anti-inflammatory activities [43]. From the results of these studies, it can be proposed that the potent activity of OPE might be due to synergistic effects of phytochemicals that are abundantly present in *Allium cepa*.

Hypoglycemic activity of Allium cepa *in high-cholesterol diet-fed diabetic animal models*

Keeping in view the antihyperlipidimic effects of SMCS, researchers [49] isolated SMCS from *Allium cepa* Linn. The antihyperlipidimic effects of SMCS in high-cholesterol diet-fed rats were investigated and its effects were compared with that of the hypolipidemic drug gugulipid. SMCS was administered at a dose of 200 mg/kg body weight for 45 d. SMCS exhibited antihyperlipidimic effects compared with high-cholesterol diet-fed rats. The fasting blood glucose did not change in any of the experimental groups. SMCS exhibited its antiatherogenic effects as that of hypolipidemic drug. SMCS and gugulipid also caused reduction of endogenous lipogenesis and increased the excretion of metabolic by-products via the intestinal tract. Although SMCS exhibited the same therapeutic effects as that of gugulipid, its dose (200 mg/kg) was very high compared gugulipid's 50 mg/kg dose.

Clinical studies of Allium cepa *on diabetic patients*

In the past several decades, *Allium cepa* has demonstrated efficacy as a remedy for reducing hyperglycemia. The effect of *Allium cepa* on healthy volunteers was investigated using 25, 50, 100, and 200 g of aqueous onion extract [50]. For glucose tolerance testing, glucose was administered with the onion extract, raw and/or boiled onions, and a dose-dependent decrease was observed in blood glucose levels. This study suggested that onion acts as an antihyperglycemic agent. In 1983, a

Table 2
Investigational studies conducted on experimental animals for antidiabetic effects of *Allium cepa*

Part/component of onion used	Experimental model	Dose	Study period	Therapeutic outcomes	References
Aqueous extract	Alloxan-induced diabetic rabbits	100 and 300 mg/kg b.wt.	30 d	Antioxidant, hypoglycemic, and diabetes-associated hepatoprotective effects	[30]
SMCS	Alloxan-induced diabetic rats	200 mg/kg b.wt.	60 d	Hypoglycemic and antioxidant effects	[39]
Onion juice	Alloxan-induced diabetic rats	1 ml/100 g b.wt.	4 wk	Antioxidant and antihyperglycemic effects; alleviation of liver and renal damage	[40]
Aqueous extract	Alloxan-induced diabetic rats	200, 250, and 300 mg/kg b.wt.	6 wk	Hypoglycemic effects in dose-dependent manner	[41]
Quercetin	STZ-induced diabetic rats	15 mg/kg b.wt.	4 wk	Antioxidant and antihyperglycemic effects. Improved β-cell integrity	[43]
Freeze-dried onion powder	STZ-induced diabetic rats	6%	12 wk	Antioxidant effects; decreased blood glucose level	[44]
Onion essential oil	STZ-induced diabetic rats	100 mg/kg b.wt.	21 d	Antioxidant, antihyperglycemic, and antihyperlipidimic effects; diabetes-associated hepatoprotective and nephroprotective effects; improved glucose tolerance	[45]
OPE	STZ-induced diabetic rats	1%	45 d	Increased antioxidant activity; decreased blood glucose levels	[46]
Onion extract	ZDF-induced diabetic rats	3% and 5%	28 d	Decreased fasting blood glucose and lipid profiles; improved HOMA-IR; increased glucose tolerance	[47]
OPE	HFD/STZ-induced diabetic rats	1%	8 wk	Increased glucose uptake, normoglycemia, and insulin sensitivity; decreased lipid profiles, oxidative, and inflammatory stress	[48]
SMCS	HCD fed-induced diabetic rats	200 mg/kg b.wt.	45 d	Antihyperlipidimic effects; antiatherogenic effects	[49]
Freeze-dried onion powder	STZ-induced diabetic rats	3%	8 wk	Antihyperglycemic, antihyperlipidimic, and antioxidant effects	[51]
Freeze-dried onion powder	STZ-induced diabetic rats	7%	5 wk	Decreased blood glucose and lipid levels; increased antioxidant activity	[55]
Fibrous root extract of Welsh onion	STZ- and AIN-93G diet-induced rats	500 mg/kg b.wt.	7 wk	Antihyperglycemic effects	[56]
Ether extract of onion juice	Normal fasted rabbits	0.25 mg/kg b.wt.	Single oral dose	Hypoglycemic effects	[57]
Extracts of dried onion powder*	Alloxan-induced diabetic rabbits	250 mg/kg b.wt.	Single oral dose	Hypoglycemic effects	[58]
Extracts of onion†	Glucose-induced hyperglycemic rabbits		–	Hypoglycemic effects	[59]

b.wt., body weight; HCD, high-cholesterol diet; HFD, high-fat diet; HOMA-IR, homeostatic model assessment insulin resistance; OPE, onion peel extract; SMCS, *S*-methylcysteine sulfoxide; STZ, streptozotocin; ZDF, Zucker diabetic fatty

* Ethanol, petroleum, chloroform, and acetone extracts of dried onion powder.

† Petroleum ether and chloroform extracts of onion.

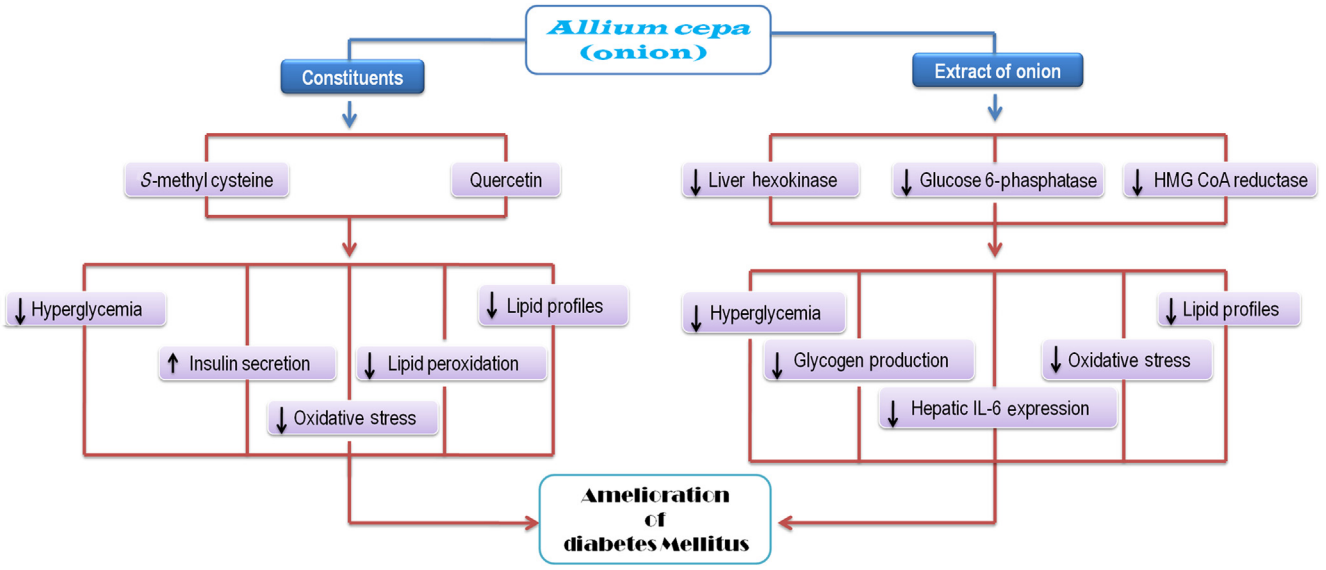

Fig. 4. Mechanism of antidiabetic action of *Allium cepa*. *S*-methylcysteine and quercetin have induced their antidiabetic effects by decreasing the onset of hyperglycemia and lipid profiles, increased antioxidant activity by reducing lipid peroxidation and oxidative stress. Extract of onion has also induced its antidiabetic effects by decreasing liver enzymes and increasing antioxidative activity. IL, interleukin.

cross-designed comparative study [51] was conducted to observe the effects of onions and green beans on patients with diabetes. Study researchers investigated the metabolic effects of diet consumed by patients with or without administration of fresh onions and green beans daily. Twenty well-controlled diabetic outpatients were randomized for a 1-wk dietary period receiving onion or non-onion diets. At the end of study period, a significant reduction in the average blood sugar level of patients receiving the onion diet compared with the levels of patients on the non-onion diet was observed [51]. Similarly, remarkable control of hyperglycemia in patients with diabetes was reported when these patients were fed the juice of *Allium cepa* along with their normal diet [52]. Moreover, it has been reported that after administering onion oil constituent to fasting normal individuals, a significant decline in blood glucose levels and an increase in insulin levels was seen [53].

Keeping in mind the dramatic hypoglycemic effects of *Allium cepa*, a clinical trial was performed with diabetic patients using the slices of *Allium cepa* [54]. In both types of diabetic patients, slices of *Allium cepa* exhibited significant antidiabetic effects, considerably reducing the levels of fasting blood glucose. Similar types of results were also obtained from the slices of *Allium cepa* when hyperglycemia was induced by glucose tolerance test.

Discussion

From the results of the studies described here, we have found that *Allium cepa* can be useful in mitigation of diabetes and the associated complications found in patients with diabetes. During the past several decades, there has been a revitalization of interest in investigating traditional health promoting the uses of onion (Table 2). The pharmacologic properties of *Allium cepa* may result from synergistic effects of constituents that are present in it. *Allium cepa* exerts its antidiabetic activity through multiple pharmacologic actions attributed to the presence of many active constituents. For instance, various experimental studies on animals showed that the antidiabetic effects of *Allium cepa* is the result of the sulfur-containing compounds isolated from onion such as *S*-methylcysteine sulfoxide [60] and *S*-allylcysteine sulpoxide [61], which can directly act on the pancreas and increase insulin levels in blood. SMCS normalizes blood glucose and lipid levels, and adjusts the activities of liver hexokinase, glucose 6-phosphatase, and HMG coenzyme-A (CoA) reductase toward normal values. The sulfur compound present in the onion can significantly control blood glucose and lipids in serum and tissues and normalize the activities of liver hexokinase, glucose 6-phosphatase, and HMG CoA reductase (Fig. 4).

Moreover, after summarizing various studies done on the hypoglycemic effects of onion, we found that *Allium cepa* exerts its antidiabetic activity despite the form in which it is administered, whether it is as an extract, oil, juice, freeze-dried powder, raw or boiled onion, or isolated active constituents of onion including quercetin and SMCS.

Allium cepa*: Mechanism of its antidiabetic activity*

As previously mentioned, depending on the constituents, *Allium cepa* shows diverse antidiabetic effects. However, *Allium cepa* has been recognized as a potent antioxidant because it contains flavonoid and organosulfur compounds [62]. Moreover, numerous studies have reported that this antioxidant property of *Allium cepa* is responsible for its various other therapeutic effects like anticancer [63,64], neuroprotective [65], and hypoglycemic [66]. Lipid peroxidation is a result of oxidative stress that could occur during various chronic diseases including diabetes. Lipid peroxidation is indicated by determining the thiobarbituric acid reactive substance [67,68]. As quercetin, a major flavonoid found in *Allium cepa*, has a strong antioxidant activity, it improves normoglycemia and decreases oxidative stress. Similarly, as mentioned previously, organosulfur constituents of *Allium cepa* normalize the levels of hexokinase, glucose 6-phosphatase, and HMG CoA reductase, and also contribute to a decrease in oxidative stress.

Conclusion

After summarizing the valuable work done on onion, it can be suggested that different parts and components of *Allium*

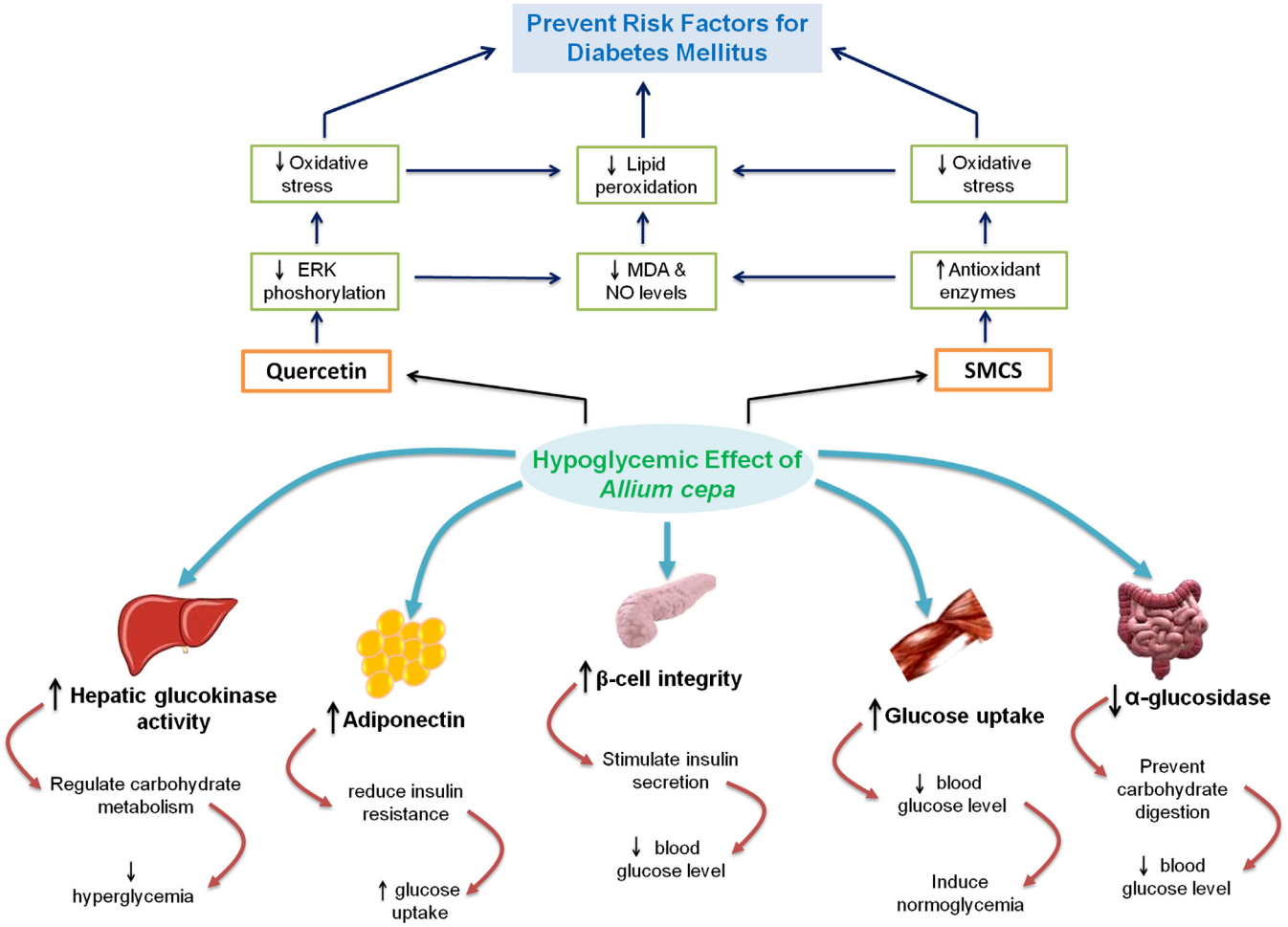

Fig. 5. Proposed mechanism for hypoglycemic effects of *Allium cepa*. MDA, malondialdehyde; NO, nitric oxide; SMCS, *S*-methylcysteine sulfoxide.

cepa, including OPE, onion essential oil, SMCS, and quercetin contribute to its hypoglycemic effect; however, the exact mechanism still remains to be elucidated. Here we would discuss the possible mechanisms through which various components of *Allium cepa* can contribute in attenuating diabetes and/or diabetes-associated complications (Fig. 5). Quercetin, being an important component, might induce hypoglycemia by inhibiting α-glucosidase and increasing adiponectin, a hormone of adipose tissue that can prevent carbohydrate digestion and reduce insulin resistance, respectively [69,70]. Moreover, quercetin can potentiate glucose-induced insulin secretion along with protecting pancreatic islets against oxidative damage by acting through phosphorylation of extracellular signal-regulated kinase [71] that has been recognized to contribute to the regulation of glucose-induced insulin secretion [72]. It is also known to increase hepatic glucokinase activity and number of pancreatic islets that contributes for improved glucose tolerance. Similarly, quercetin may provide protection against oxidative damage by decreasing MDA and nitric oxide reducing lipid.

Future perspective

Further work is needed to investigate the therapeutic potential of the active constituents of *Allium cepa*, requiring studies of various parameters that might help to investigate the exact mechanism of hypoglycemic effect of *Allium cepa*. Patients with diabetes should be clinically counseled and educated about the pharmacologic benefits of *Allium cepa* and also should be advised to increase dietary supplementation of onion for the management of DM. Through our current work we hope this dietary bulb can be recognized for its worth as a medicinal supplement against diabetes and/or diabetes-associated risk factors, as it comprises active components that have been recognized effective in improving insulin secretion, maintaining glucose tolerance and β-cell integrity by reducing oxidative damage.

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